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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/55, 31/535, 31/495
A61K 31/50, 31/47, 31/445
C07D 415/00, 213/62, 401/00
C07D 413/00, 417/00, 419/00
C07D 403/00, 405/00, 409/00
C07D 217/06, 217/12, 411/00
C07D 421/00

A1

(11) International Publication Number: **WO 93/04684**

(43) International Publication Date: 18 March 1993 (18.03.93)

(21) International Application Number: PCT/US91/09082

(22) International Filing Date: 20 December 1991 (20.12.91)

(30) Priority data:
757,881 11 September 1991 (11.09.91) US

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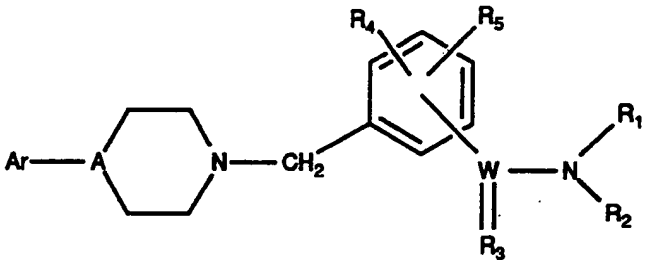
(81) Designated States: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MW, NO, RO, SD, SU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL 4-ARYLPIPERAZINES AND 4-ARYLPIPERIDINES



(I)

(57) Abstract

Compounds of the general formula (I) are disclosed as novel antipsychotic agents.

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Novel 4-Arylpiperazines and 4-Arylpiperidines

BACKGROUND OF THE INVENTION

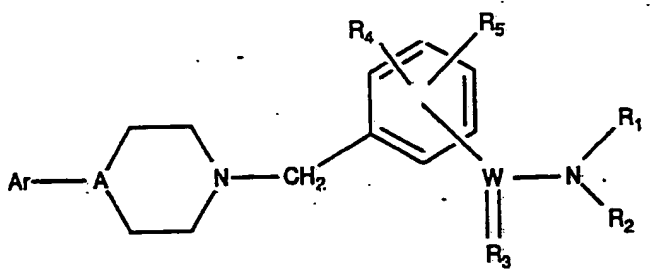
Antipsychotic drugs are known to alleviate the symptoms of mental illnesses such as schizophrenia. Examples of such drugs include phenothiazine derivatives such as promazine, chlorpromazine, fluphenazine, thioridazine and promethazine, thioxanthenes such as chlorprothixene, butyrophenones such as haloperidol, and clozapine. While these agents may be effective in treating schizophrenia, virtually all except clozapine produce extrapyramidal side effects, such as facial tics or tardive dykinesia. Since antipsychotics may be administered for years or decades to a patient, such pronounced side effects may complicate recovery and further isolate the individual from society.

Compounds having some structural similarity to those of the present invention are described in EPO application 88,309,581.2, U. S. Patent Nos. 4,772,604; 4,782,061; 4,362,738; 3,988,371; 4,666,924; 4,931,443; and 4,992,441. Other somewhat similar compounds are disclosed in *J. Clin. Chem. Clin. Biochem.* **1988**, *26*, 105.

The present invention describes novel compounds that combine antipsychotic effects with minimal or reduced side effects such as extrapyramidol symptomology, and increased acid stability relative to some of the compounds known in the art.

SUMMARY OF THE INVENTION

Compounds of the general formula I:

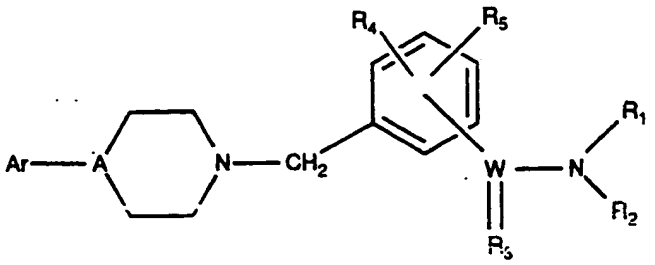


I

wherein Ar, W, A, R_1, R_2, R_3, R_4, and R_5 are as defined hereinafter, are potent antipsychotic agents. Many of these exhibit a reduced tendency to induce extrapyramidal side effects and/or improved acid stability when compared with prior art compounds. The compounds of the present invention may also be useful in the treatment of other disorders of the central nervous system such as anxiety and aggression. In addition, certain of the compounds represented by formula I are useful in the treatment of constipation, diarrhea, emesis, and hypertension.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds represented by the general formula I:



I

A is N or CH.

W is C or SO.

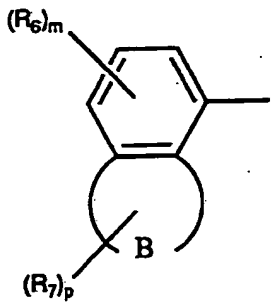
R_3 is O or S where W is C; R_3 is O where W is SO.

R_1 and R_2 are independently selected from any one of H, C_1-C_8 alkyl, phenyl, substituted phenyl, aralkyl wherein the alkyl portion is C_1-C_8, C_1-C_8 acyl C_4 to C_8 cycloalkyl; or $-NR_1R_2$ may be taken together to form a ring having 4-10 ring atoms, preferably 5-8 ring atoms, which ring may be saturated or unsaturated, preferably saturated, substituted or unsubstituted, and may contain one or more hetero atoms in addition to the ring N, such as S, O or N within the ring; or $-NR_1R_2$ may be taken together to form a fused ring system containing 8 to 12 ring atoms and may contain one or more hetero atoms in addition to the ring N, such as S, O or N, which ring may be saturated or unsaturated, substituted or unsubstituted; or NR_1R_2 may be taken together to form a spiro ring system which may be saturated, preferably saturated, or unsaturated, substituted or unsubstituted, and may contain one or more hetero atoms in addition to the ring N, such as S, O or N within the ring.

R_4 and R_5 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, halogen, haloalkyl, C_1-C_8 alkylthio, amino, or C_1-C_8 alkyl amino.

Ar is phenyl, heteroaryl or substituted phenyl wherein phenyl may be independently substituted with one or more of H, C_1-C_8 alkyl, cycloalkyl, hydroxyalkyl, C_1-C_8 alkoxy, aryloxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkylthio, halogen, nitro, C_1-C_8 haloalkyl, amino or C_1-C_8 mono- or di-alkylamino. Alkoxy, such as i-propoxy or methoxy is presently the preferred substituent. As a halogen, the substitution is preferably fluorine, chlorine, or bromine. Optionally present hydroxyl or hydroxyalkyl groups may be esterified or etherified. Examples of suitable heteroaryl rings are pyrimidinyl, pyridinyl, pyridazinyl, pyrazinyl, imidozyl, pyrrole, furan, thiophene, triazolyl, and thiazolyl.

Ar may also be a fused ring system of the formula II:



II

wherein B together with the 2 carbon atoms of the phenyl group forms an entirely or partly unsaturated cyclic group having 5-7 ring atoms and within the ring 1-3 hetero atoms from the group O, S and N may be present with the proviso that the sum of the number of oxygen atoms and sulfur atoms is at most 2, and that the nitrogen atoms in the ring may be substituted with R_8 selected from any one of H, C_1-C_8 alkyl, hydroxyalkyl or C_1-C_8 acyl;

R_6 and R_7 may be independently selected from any one of alkyl, cycloalkyl, optionally substituted phenyl or heteroaryl, hydroxyalkyl, alkoxyalkyl, alkoxy. aryloxy, alkylthio, arylthio, mono-or di-alkylamino, mono- or di-arylamino, hydroxyl, amino, alkyl, alkoxy, amino, or mono- or di-alkylaminocarbonyl, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, amino or mono- or di-alkylaminosulphonyl. R_8 may also be an oxo or thioxo group. Variable m has the value 0-3 and p has the value 0-2.

More preferred values for the moiety of formula II are:

B forms together with the two carbon atoms of the phenyl group an entirely or partly unsaturated ring consisting of 5 atoms, which ring comprises at least one oxygen atom. R_6 and R_7 are alkyl, alkoxy, hydroxyl, nitro, cyano, halogen, or trifluoromethyl. Variables m and p have the value 0-2. A particular subgensis of such compounds are those wherein m and p each have a value of 0.

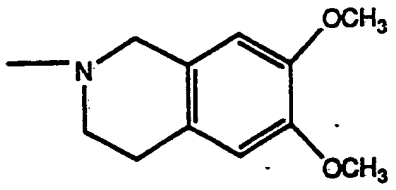
When R_6 or R_7 comprises an alkyl group, it is preferably a straight or branched alkyl group having 1-5 carbon atoms. As a cycloalkyl group, the groups R_6 or R_7 comprise a ring system having 3-7 ring atoms and not more than 10 carbon atoms including any substituents as a whole. When R_6 or R_7 is a hydroxyalkyl group such a group preferably comprises 1-5 carbon atoms. As a halogen atom, R_6 or R_7 preferably is fluorine, chlorine or bromine. Optionally present hydroxyl or hydroxyalkyl groups may be esterified or etherified.

When R_1, or R_2 is substituted phenyl it may be substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, halogen, trifluoromethyl, C_1-C_8 alkylthio, dialkylamino (wherein each alkyl is C_1-C_8), C_1-C_8 alkylamino, nitro or mono or di-alkylamino sulphonyl (wherein each alkyl is C_1-C_8).

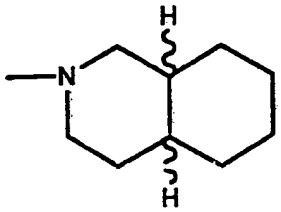
When $-NR_1R_2$ are taken together to form a ring, a fused ring system or a spiro ring system, such rings may be substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, phenyl, substituted phenyl (wherein phenyl may be substituted with any of the substituents listed for R_1 or R_2 substituted phenyl), hydroxy, aralkyl such as benzyl, wherein the alkyl portion is C_1-C_8, oxo or thioxo.

Examples of preferred ring systems wherein $-NR_1R_2$ are taken together to form a ring having 4-10 ring atoms include pyrrolidine, piperidine, hexahydroazepine, octahydroazocine, oxazine and 2,6-dimethylpiperidine.

Examples of preferred fused ring systems for $-NR_1R_2$ are represented by formulas III and IV:

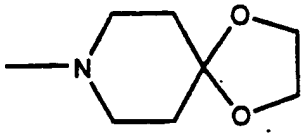


III



IV

As used herein for the definition of $-NR_1R_2$, a spiro ring is a 2 ring system, the union of which is formed by a single atom which is the only common member of the two rings. A particularly preferred spiro ring is represented by the formula V:

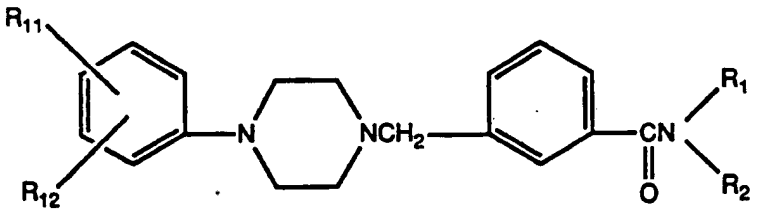


V

The term alkyl unless otherwise specified is used herein to represent branched and unbranched alkyl groups. With reference to substituents, the term independently means that when more than one of such substituent is possible such substituents may be the same or different from each other.

Compounds according to this invention have a 1,2-, 1,3- or 1,4- relationship of the W substituent with the $-CH_2-$ group on the W-bearing phenyl ring. Preferred compounds have a 1,2- or 1,3- relationship of these two groups. The R_4 and R_5 substituents may be located in any of the other unsubstituted ring positions.

A particularly preferred subgenus of compounds of the formula I are those of the formula (Ia):



Ia

wherein R_1 and R_2 are as defined above and R_{11} and R_{12} are as defined as substituents for Ar in formula I. Preferably R_1 and R_2 are taken together with the N to form a saturated ring having 5-8 ring atoms and one of R_{11} and R_{12} is C_1-C_8 alkoxy and the other is H. The most preferred C_1-C_8 alkoxy group is i-propoxy.

Examples of particularly preferred compounds include:

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine succinate;

Hexahydro-1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-benzoyl]-1H-azepine monohydrochloride;

1-[3-[[4-(1,4-Benzodioxan-5-yl)-1-piperazinyl]methyl]benzoyl]piperidine perchlorate (5:7);

1-[2-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine dhydrochloride;

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]-benzoyl]-2,6-dimethylpiperidine hydrochloride (3:2); and

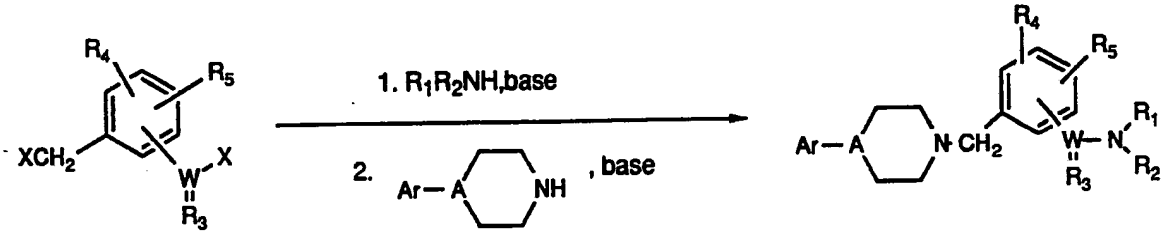
1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperidinyl]methyl]benzoyl]-piperidine monohydrochloride.

The invention definition of formula I includes racemates and individual isomers, e.g. as caused by the presence of a stereogenic carbon such as when a substituent would be 2-butyl. Also within the scope of the invention are compounds of the invention in the form of hydrates and other solvate forms.

perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicyclic, p-amino-salicyclic, 2-phenoxybenzoic, 2-acetoxybenzoic or a salt made with saccharin. Such salts can be made by reacting the free base of formula I with the acid and recovering the salt.

The compounds of formula I may be prepared according to Reaction Scheme 1:

Reaction Scheme 1



X = Cl, Br

VI

VII

I

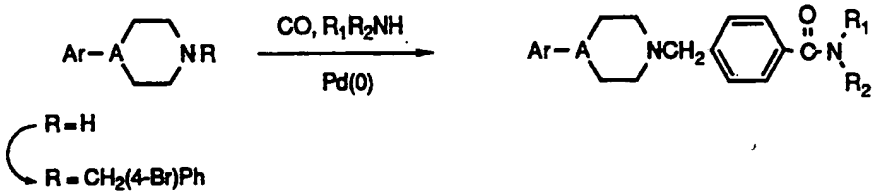
As shown, the 1,2-, 1,3, and 1,4-disubstituted benzamides or sulfonamides may be prepared by a sequential reaction with the appropriate halomethyl benzoyl halide or halomethyl benzenesulfonyl halide. The first

As shown, the 1,2-, 1,3, and 1,4-disubstituted benzamides or sulfonamides may be prepared by a sequential reaction with the appropriate halomethyl benzoyl halide or halomethyl benzenesulfonyl halide. The first condensation with the requisite amine is conducted in a non-protic solvent such as tetrahydrofuran (THF) with cooling (e.g. in the range -78°C to 5°C), being careful not to let the solution exotherm so as to avoid reaction of the halomethyl functionality. The base present in the reaction (for the removal of the HX formed) is typically a tertiary amine such as triethyl amine or di-isopropyl ethyl amine, or it could be a molar excess (at least) of the amine reactant (e.g. R_1R_2NH). The intermediate halomethyl benzamide thus formed could be then taken on directly to the product by reaction with the aryl piperazine, or it could be isolated after an extractive workup and/or chromatography. If the intermediate was carried out in situ to the product in THF, heating (30°C-67°C) is generally required for complete reaction. If the intermediate is isolated and then reacted separately with the aryl piperazine, the optimal solvents are dipolar aprotic solvents such as dimethylformamide (DMF) or N-methyl-2-pyrrolidinone. The base used in this latter step could be a tertiary amine or potassium or sodium carbonate. Using the two-step method (i.e. isolation of the intermediate), the product could in some cases be obtained pure after recrystallization as a salt without resorting to chromatography.

The 1,2- and 1,3-halomethylbenzoyl halides are commercially available from Fluka, Carbolabs or Pfaltz and Bauer or could be prepared by literature methods or modifications thereof. (See e.g.: Ger. Offen. 2,835,440, 28 Feb. 1980; and J. Johnson and I. Pattison *J. Hetero. Chem.* **1986**, *23*, 249). Halomethyl benzoyl halides bearing substituents have also been described in the literature, such as in the methoxy-substituted case cited in R. Quelet et al.

The 1,3- or 1,4-disubstituted analogs may be prepared as described above. There are, however, alternative methods for the preparation of compounds of this type. For example, they may be synthesized by a palladium-mediated coupling of a bromobenzyl derivative with carbon monoxide and piperidine (*J. Org. Chem.* **1974**, *39*, 3327) as shown in Reaction Scheme 2 for a 1,4-disubstituted case.

Reaction Scheme 2

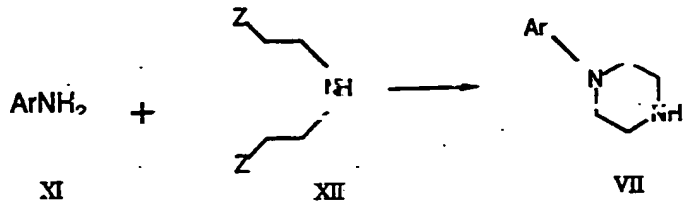


IX X

The preparation of the sulfonamide analogues requires preparation of the necessary halomethyl sulfonyl halide by halogenation of the appropriate toluenesulfonyl halides on the benzylic methyl position with N-bromosuccinimide mediated by benzoyl peroxide. The halomethyl sulfonyl halides were used in generally the same manner as in the benzoyl halide case.

The aryl piperazines are commercially available from Aldrich Chemical Company or may be prepared by standard methods known in the art (for example see G. E. Martin et al. *J. Med. Chem.* **1989**, *32*, 1052). These piperazines (VII) may be obtained according to the following Reaction Scheme 3 where Ar is as described in connection with formula I and Z is a leaving group such as halo (e.g. chloro):

Reaction Scheme 3 12



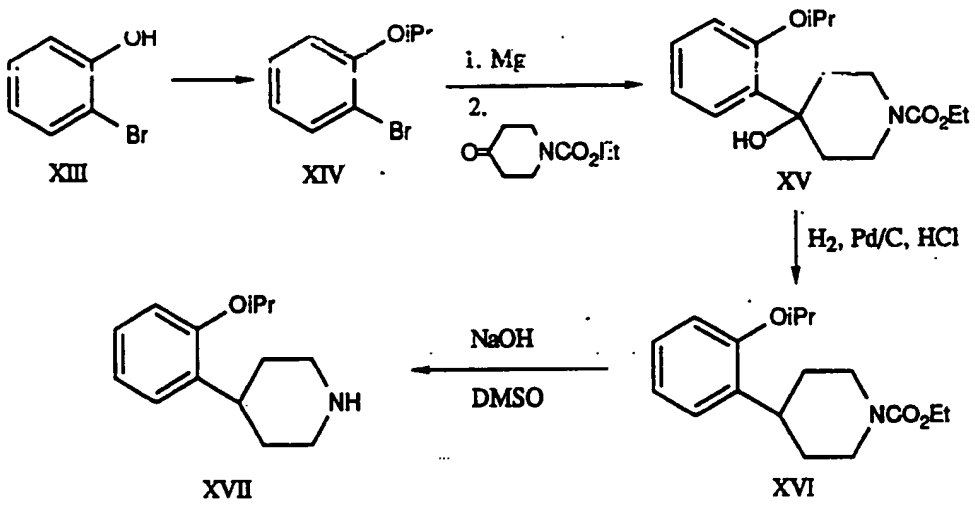
XI XII VII

In carrying out Reaction Scheme 3, an amine XII is heated with an aniline or an aromatic heterocyclic primary amine XI at about 50 to 150°C in a solvent such as n-butanol with recovery of the piperazine VII.

Piperazines of formula VII where Ar is a formula II moiety are described as formula (2) in U.S. Patent 4,782,061 published earlier as EPO 185,429 and EPO 190,472 on June 15, 1986 and August 13, 1986, respectively, which documents are hereby incorporated by reference. Other piperazines of formula VII where Ar is a formula II moiety are described as formula 29 in EPO 138,280 published April 24, 1985 which is incorporated by reference.

The piperazine employed for the preparation of compounds #3 and 4 in Table 3 was prepared by the method of I. van Wijngaarden et al. (*J. Med. Chem.* **1988**, *31*, 1934). The piperidine used in the preparation of compounds #22-25 was prepared by the method shown in Reaction Scheme 4.

Reaction Scheme 4

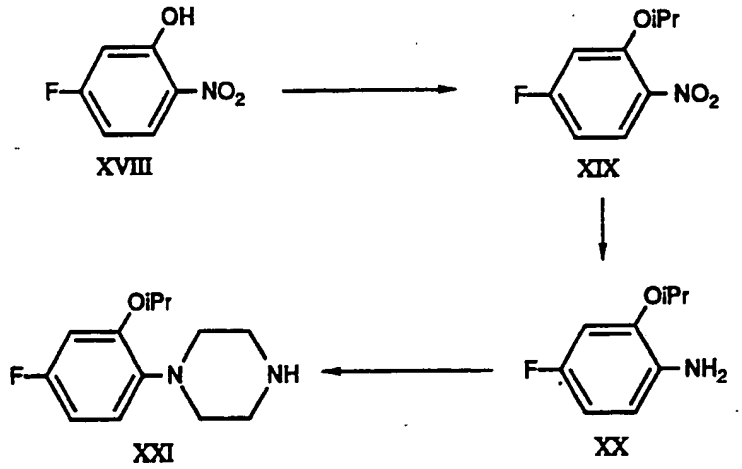


5

The piperazine utilized for the synthesis of compounds #62-64 was synthesized as shown in Reaction Scheme 5.

Reaction Scheme 5

10



The antipsychotic activity of the compounds of the invention may be determined by the Block of Conditioned Avoidance Responding (Rat) test (CAR), references being Cook, L. and E. Weidley in *Ann. N.Y. Acad. Sci.*, **1957**, *6*, 740-752, and Davidson, A. B. and E. Weidley in *Life Sci.*, **1976**, *16*, 1279-1284. This test was performed for compounds disclosed in this invention, and the data is listed in Tables 1-6. In addition the affinity of the compounds for several receptors found in the central nervous system was evaluated; the affinity for the D-2 (dopamine-2) receptors is also listed in Tables 1-6. As modulation of this receptor is known to be beneficial in the treatment of schizophrenia, affinity for this receptor indicates potential utility for the compounds. A D-2 affinity of 125 nM or less has been taken as predictive of antipsychotic activity, if a suitable means of administration could be developed which would target the compound to the site of action (brain). As a class, the compounds of the present invention also display a remarkably low cataleptogenic response in rats. The catalepsy test is often taken to evaluate the liability of anti-psychotics to produce extra-pyramidal side effects. Representative data for several of the preferred compounds at a single dose is given in Table 8. The only compounds which to date have not exhibit antipsychotic activity in either of the screens in which they have been tested are compound #9, 10, 31, 32, 34 and 49. Of these, only compound #31 and 32 have not exhibited activity in any of the other non-antipsychotic screens in which they have been tested to date.

Compound #36 and 37 have been found to be particularly potent inhibitors of apomorphine-induced emesis in the dog, and that data is shown in Table 7. This latter test is used in the preclinical evaluation of antipsychotics, and it also implies that the compounds could be used clinically for the treatment of emesis.

Certain of the compounds of the present invention also have been demonstrated to be useful in the treatment of constipation and in the treatment of diarrhea and/or irritable bowel syndrome as shown in Table 9. The test used to determine this activity is a Rat Glass Bead Test, described below.

Compound #10 and 71 were also evaluated in the fully recovered, unanesthetized, unrestrained spontaneously hypertensive rats (SHR model) which is described hereinafter. They were deemed to be active because at doses of 30 mg/kg p.o. they caused a drop in the mean arterial pressure. For compound #10 the drop was 26 mm of mercury with an onset of 0.5 h and a duration of 3.5 h. For compound no. 71 the drop was 37 mm of mercury with an onset of 0.25 h and a duration of 5.75 h.

Block of Conditioned Avoidance Responding (Rat)

Apparatus: Rat operant chambers, housed within sound attenuated booths, both from Capden Instruments Ltd., were used in this test. The test chamber (8" H x 90-3/8" W x 9" D) is constructed of aluminum and plexiglass with floor grid bars of stainless-steel (1/8" O.D.) spaced 9/16" apart. A stainless-steel operation level 1-1/2" wide projects 3/4" into the chamber and is positioned 2-2/8" above the grid floor. The shock stimulus is delivered via the grid floor by a Coulbourn Instruments solid state module. The parameters of the test and the collection of data are controlled automatically.

Training: Male, Fischer 344 rats obtained from Charles River (Kingston, NY) weighing more than 200 g, are individually housed with chow and water

provided ad libitum. The rats are trained for two weeks to approach criterion levels in the avoidance test (90% avoidance rate). One-hour training sessions are run at about the same time each day for four or five days a week. The training session consists of 120 trials, with the conditioned stimuli presented every 30 sec. A trial begins with presentation of the conditioned stmuli (a light and a tone). If the rat responds by depressing the operant lever during the 15-second presentation of the conditioned stimuli, the trial is terminated and the animal is credited with a CAR. Failure to respond during the conditioned stimuli causes the presentation of the unconditioned stimulus, a 0.7 mA shock which is accompanied by a light and tone for five seconds. If the rat depressed the lever within the ten-second period, the shock and trial are terminated and an escape response recorded. If the rat fails to depress the lever during the UCS (shock), the trial is terminated after ten seconds of shock and the absence of a response is scored as a failure to escape. Intertrial level presses have no effect. If a rat performs at the 90% CAR level for two weeks, it is then run twice a week on the test schedule (see below) until baseline performance stabilized. Before any drug is administered, two weeks of CAR at a rate of 90% or better is required.

Determination of ED_{50} Values

Trained rats are run in a one-hour session on two consecutive days at the same time and in the same test chamber each day. The sessions consist of 60 trials, one every minute. The conditioned stimuli are presented for 15 sec (maximum) and the unconditioned stimuli five sec (maximum). On Day 1, a vehicle solution is administered to the rats at a time preceding the trial run corresponding to the pretreatment time for the test compound. The route of administration and the volume of vehicle are also matched to that of the test

compound. Only animals that exhibited greater than 90% CAR on Day 1 are given the test compound on Day 2.

Statistical Computations: ED_{50} values (that dose required to reduce the mean number of CARS to 50% of the control mean) are determined in the following manner. The percent change in CAR on the drug treatment day compared to vehicle pretreatment day is the key measure. The percent change (% change) in CAR is determined using the following formula:

% change CAR = ((Day 2 % CAR/Day 1 % CAR) x 100)-100

A negative number indicates a blockade of CAR, whereas a positive number would indicate increased CAR. The test results are reported as the mean % change for the group of rats. A reading of -20% is generally taken to represent a minimum value for a compound to be designated as active at a given dose in the CAR test. Failure to escape was calculated for each animal as follows:

% Failures = # of Failures to Escape/# of trials

The % failures, viz., loss of escape, is also reported as a group mean. Failures to escape are monitored closely and a session is terminated if ten failures occurred. ED_{50} values and 95% confidence limits are calculated using linear regression analysis. The results of the CAR test is shown in Tables I-6.

In the Tables, i-Pr is isopropyl, Et is ethyl, Ph is phenyl, n-Bu is normal butyl, cC_6H_{11} is cyclohexyl, BOC is t-butyloxycarbonyl, and Ac is acetyl. The escape loss numbers are shown at CAR 5 mg/kg unless otherwise noted.

Receptor Binding Assay

The dopamine D_2 binding activity of compounds was determined using a P_2 fraction (synaptosomal membranes) prepared from male, Wistar rats. The D_2 assay employed a P_2 fraction from the striatum, the ligand ^{3}H-spiperone at a concentration of 0.05 nM, and 1 mM haloperidol as a blank determinant. Incubation was in 3 mM potassium phosphate buffer for 45 min at 37°C. Under these conditions, specific binding constituted 75% of total binding, and the K_I values for some known drugs were: 0.37 nM for haloperidol and 82 nM for clozapine.

The data from this assay were analyzed by calculating the percent inhibition of the binding of the tritiated ligands by given concentrations of the test compound. K_I values, where given, were obtained from the logit analysis of concentration-inhibition curves.

Block of Apomorphine-Induced Emesis In Dogs

This procedure was modified from that described in Janssen, P. A. J.; Niemegeers, C. J. E.; Schellekens, K. *Arzn.-Forch.* **1965**, *15*, 1196-1206. The animals were treated with a test dose of apomorphine HCl to produce retching, and the effectiveness of a test compound in blocking that retching is determined. This effectiveness is normally a consequence of dopamine

antagonism (Niemegeers, C. J.; Janssen, P. A. J. *Life Sciences.* **1976**, *24*, 2201-2216). Animals were deprived of food for at least 16 h before testing, but they were allowed free access to water. Following one of several pretreatments, a challenge dose of 1 mg/kg apomorphine HCl s.c. was given and the number of retches that occurred during the following 20 min period was recorded. At the start of the series, and after one week on testing, all dogs were pretreated with saline before the challenge dose of apomorphine HCl was administered. All of the saline-pretreated animals retched. During the course of the study; each dog was tested between 5 and 11 times with 2-21 days between testing. Data were analyzed to determine the ED_{50} dose for blocking apomorphine HCl-induced emesis. The dose calculated to block retching in 50% of the animals and the 95% confidences limits was determined with PROBIT analysis.

Catalepsy Test in Rats

The catalepsy test was performed as described in Clineschmidt, B. V.; McKenry, M. A.; Papp, N. L.; Pflueger, A. B.; Stone, C. A.; Totaro, J. A.; Williams, *M. J. Pharm. Exp. Therap.* **1979**, *208*, 406-476. The forepaws of male, Sprague-Dawley rats obtained from Charles River (170-240 g) were gently placed on a black cork (3.5 cm high) and the time until the forepaw was removed was recorded. Each rat was given three trials with a maximum time of 60 sec on the cork. The sum of the three trials was taken as the score for each rat. Percent catalepsy was defined as the percent of 180 sec (maximum time) that a rat permitted its forepaw to rest on the cork. Pretreatment times of 60 min and 240 min were used on a routine basis. In each test session, two control groups were used; animals treated with saline (or vehicle) served as a negative

control and animals treated with haloperidol were a positive control. The dose-response relationship for a compound was determined at the time of maximum catalepsy (60 or 240 min). The results of this test are shown in Table 8.

Rat Glass Bead Test

The rat glass bead test is used to evaluate the action of compounds on propulsive motility of the distal colon. Male Charles-River rats weighing 50-90 grams are fasted for at least 18 hours in individual cages with water provided. Groups of rats are then dosed by the indicated route at the appropriate pretreatment time. A 4 mm glass bead is then inserted 3.5 cm into the distal colon through the anus using a 4 mm diameter glass rod. Rats are then placed in open top glass jars and observed for 60 minutes. The time for expulsion of the bead is noted for each rat. Rats not expelling the bead after 60 minutes are necropsied and the presence of the bead in the colon confirmed. Expiration times of 0-15 min signify potential use in the treatment of constipation. Values of 40-60 min suggest utility in the treatment of diarrhea. Values of 16-39 are taken to show inactivity in this test. Data are presented as mean expulsion times and standard error of the means in Table 9. Statistical analysis is done using one way analysis of variance and Fisher's LSD comparison. A probability of less than 0.05 is considered to be statistically significant.

Spontaneously Hypertensive Rat Test (SHR)

Adult male 350-450 g SHR [Tac:N(SHR)FBR], Taconic Farms, Germantown, New York are prepared for direct measurement of arterial pressure, housed in individual cages, and maintained on constant intraarterial

infusion to assure catheter patency. Rats are permitted a 7-day postoperative recovery period to allow complete restoration of salt/water balance and body weight. Rats are assigned to vehicle or drug treatment groups (n=3/group). Drugs are uniformly suspended in 1% methylcellulose vehicle and given orally by gavage. Parameters are sampled continuously from the conscious, unrestrained rats and averaged every 15 min for the first 2 h and then hourly through 24 h after dosing. In order to take diurnal changes that are not drug related into account, 24 h timecourse curves for each parameter in drug treated SHR are compared to those from the concurrent control group. Since the average standard between-subject error is about 5 mm of mercury for arterial pressure parameters and about 11 bpm for heart rate, differences from concurrent control of greater than 10 mm of mercury and 22 bpm (2 SEM) are considered drug-related activity. Onset and duration are calculated from any pattern that achieves a maximum difference that meets these criteria.

To prepare the pharmaceutical compositions of this invention, one or more compounds or salts thereof of the invention, as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders,

disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, from about 50 to about 100 mg of the active ingredient.

In therapeutic use as an antipsychotic agent, the compounds of this invention may be administered in an amount of from about 0.5 to 5 mg/kg per day, and more preferably 1-3 mg/kg per day. The dosages, however may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following Examples illustrate the present invention, but are not deemed to be limiting. Examples 1, 6, and 10-14 describe the preparation of specific compounds listed in the Tables which follow the Examples, whereas the other Examples describe the preparation of intermediates described in the reaction schemes.

SPECIFIC EXAMPLES:

EXAMPLE 1

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine Hydrochloride (3:2) (CP #36)

A solution of 3-(chloromethyl)benzoyl chloride (6 mL, 42.3 mmol) in 70 mL of THF was treated with diisopropylethylamine (33.1 mL, 0.19 mol). This solution was cooled in an acetone/dry ice bath and treated with piperidine (4.18 mL, 42.3 mmol) over a period of 2 min. After 5 min, the ice bath was removed, and the solution was allowed to warm to ambient temperature. After a total of 1 h, N-(2-isopropoxyphenyl)piperazine fumarate (14.45 g, 43 mmol) was added. The solution was stirred at ambient temperature overnight, and then at reflux for 7 h. The solution was allowed to cool to ambient temperature, then treated with water and methylene chloride. The organic layer was withdrawn, dried ($MgSO_4$), and filtered. The product was purified on silica gel (EtOAc/hexane, 6:4), dissolved in iPrOH, treated with concentrated HCl (ca. 2.5 mL), and then triturated with ethyl ether. The resultant solid was recrystallized from iPrOH/ethyl ether to give 9.1 g (45%) white powder, mp 222-227°C. The ^1H NMR in $CDCl_3$ supported the assigned structure.

Elemental Analysis: Calculated for $C_{26}H_{35}N_3O_2 \cdot 1.5HCl$: C, 65.57; H, 7.72; N, 8.82; Cl, 11.17. Found: C, 65.77; H, 7.89; N, 8.78; Cl, 11.07.

Compound #2-10, 22-27, 29-49, 52-56, 58-69, 71-80, and 82 were prepared by the use of the general method described for Example 1 or slight alterations of it, with the necessary modifications in the choice of the initial amine starting material, (3-chloromethyl)benzoyl chloride, and aryl piperazine or aryl piperidine. Specifically, compound #2 was prepared by replacing

(3-chloromethyl)benzoyl chloride with 2-methoxy-5-(chloromethyl)benzoyl chloride. Compound #3 required the use of 7-(N-piperazinyl)benzofuran instead of N-(2-isopropoxyphenyl)piperazine (IPP). Compound #4 required the use of 7-(N-piperazinyl)benzofuran and homopiperidine instead of IPP and piperidine. Compound #5 used 3-(N-piperazinyl)benzothiazole instead of IPP. The preparation of compound #6 entailed the use of 5-(N-piperazinyl) benzodioxane instead of IPP. Compound #7 required the use of 5-(N-piperazinyl)benzodioxane instead of IPP and homopiperidine instead of piperidine. Compound #8 was synthesized with 1-(N-piperazinyl)naphthalene instead of IPP.Compound #9 required N-[3,4-(methylenedioxy)phenyl] piperazine instead of IPP. The preparation of compound #10 used 2-(N-piperazinyl)pyrimidine instead of IPP. Compound #22 required the use of XVII instead of IPP. Compound #23 required the use of XVII instead of IPP and homopiperidine instead of piperidine. Compound #24 required the use of XVII instead of IPP and cis-2,6-dimethylpiperidine instead of piperidine. Compound #25 required the use of XVII instead of IPP and morpholine instead of piperidine. Compound #26 required the use of 4-carbethoxypiperidine instead of piperidine. Compound #27 required the use of N-(methyl)phenethylamine instead of piperidine. Compound #29 required the use of 1,4-dioxa-8-azaspiro[4.5]decane instead of piperidine. Compound #30 required the use of N-(2,5-dimethoxyphenyl)piperazine instead of IPP. Compound #31 required the use of N-(2,5-dimethoxyphenyl) piperazine instead of IPP, and pyrrolidine instead of piperidine. Compound #32 required the use of N-(2,6-dimethoxyphenyl) piperazine instead of IPP. Compound #33 required the use of N-(3-nitrophenyl)piperazine instead of IPP. Compound #34 required the use of IPP instead of piperidine. Compounds #35, 37, 38, 39, and 40 required the replacement of piperidine with pyrrolidine, homopiperidine, azacyclobutane,

azacyclooctane, and morpholine respectively. Compounds #41, 42, 43, 44, and 45 required the replacement of piperidine with 3,3-dimethylpiperidine, 4-methylpiperidine, cis-2,6-dimethylpiperidine, 1,2,3,4-tetrahydro-6,7-(dimethoxy)isoquinoline, and tetrahydroisoquinoline respectively. Compounds #46, 47, and 48 required the replacement of piperidine with N-(phenyl)piperazine, N-(carbethoxy)piperazine, and N-(benzyl)piperazine respectively. Compound #49 required the use of N-(3-trifluoromethylphenyl)piperazine instead of both IPP and piperidine. Compounds #52, 53, 54, 55, and 56 required the replacement of piperidine with diethylamine, dibutylamine, N-(methyl)butylamine, cyclohexylamine, and N-(methyl)cyclohexylamine respectively. Compounds #58, 59, 60, and 61 required the replacement of piperidine with N-(methyl)benzylamine, 4-fluoroaniline, 2-aminomethyl-N-ethylpyrrolidine, and ammonia respectively. Compound #62 required the use of XXI instead of IPP. Compound #63 required the use of XXI instead of IPP and homopiperidine instead of piperidine. Compound #64 required the use of XXI instead of IPP and morpholine instead of piperidine. Compound #65 required the use of N-(2-propylphenyl)piperazine instead of IPP. Compound #66 required the use of N-(2-propylphenyl)piperazine instead of IPP and homopiperidine instead of piperidine. Compound No. 67 required the use of N-(2-ethoxyphenyl)piperazine instead of IPP and homopiperidine instead of piperidine. Compound No. 68 required the use of N-(2-methoxyphenyl)piperazine instead of IPP. Compound No. 69 required the use of N-(2-methoxyphenyl)piperazine instead of IPP and homopiperidine instead of piperidine. Compounds #71, 72, 73, 74, 75, and 76 required the replacement of IPP with N-(4-chlorophenyl)piperazine, N-(2-trifluoromethylphenyl)piperazine, N-(2-chlorophenyl)piperazine, N-(2-

cyanophenyl)piperazine, N-(3-chlorophenyl)piperazine, and N-(3-trifluoromethylphenyl)piperazine respectively. Compound No. 77 required the use of N-(2-chlorophenyl)piperazine instead of IPP. Compounds #78 and 79 required the replacement of IPP with N-(3,5-dichlorophenyl)piperazine and phenylpiperazine respectively. Compounds #80 and 81 required the replacement of piperidine with 3-azabicyclo[3.2.2]nonane and N-(t-butyloxycarbonyl)-1,6-diaminohexane respectively.

In addition, compound #81 was prepared from compound #82 by treatment with *p*-toluenesulfonic acid in methanol in a standard solvolysis reaction for removal of the *t*-butyloxycarbonyl group. In a similar manner, compound #28 was prepared by acidic solvolytic removal of the ketal group of compound #29.

EXAMPLE 2

1-Bromo-2-(1-methylethoxy)benzene (XIV)

A mixture of *o*-bromophenol (23.2 mL, 0.20 mol), potassium carbonate (33.2 g, 0.24 mol) and 2-bromopropane (28.0 mL, 0.30 mol) in dimethylformamide (200 mL) was stirred in a preheated oil bath (60°C) for 5 h. The cooled reaction mixture was then partitioned between ether and water. The layers were separated and the aqueous phase was extracted with ether. The combined organic solution was washed with copious amounts of water, 3N aqueous NaOH, dried ($MgSO_4$), filtered and concentrated in vacuo to furnish 39.3 g (91%) of XIV as a pale yellow oil which was carried on without further purification. The structure was supported by GC/MS and 90 MHz ^{1}HNMR.

EXAMPLE 3

1-Carbethoxy-4-[2-(1-methylethoxy)phenyl]-4-piperidinol (XV)

To a suspended solution of Mg chips (10.07 g, 0.414 mol) in anhydrous ether (150 mL) at 22°C under Argon atmosphere was added ca. 0.15 mL of 1,2-dibromoethane. Then 43.7 g (0.200 mol) of XIV in 200 mL of ether was added dropwise. After 50% of the aryl halide was added, the reaction began to reflux vigorously. The flask was cooled in an ice bath. After the refluxing had subsided somewhat, the ice bath was removed and the remaining aryl halide was added over a 1.5 h period. The resultant Grignard reagent was cooled in a dry ice/ether bath for 2 h and then treated with 34.0 mL (0.221 mol) of 98% 4-carbethoxy-1-piperidone. Upon complete addition of ketone, the reaction mixture was allowed to warm to 22°C and stirred for 2 h. The reaction was then quenched with cold aqueous ammonium chloride which resulted in an emulsion. Addition of 1M aqueous HCl solution separated the two layers. The aqueous phase was extracted with additional ether and the combined organic solution was washed with 10% aqueous sodium bisulfite, 1.0 M HCl, saturated $NaHCO_3$, and dried (K_2CO_3). Filtration and concentration yielded 56.36 g of XV as a yellow viscous oil which was carried on without further purification The structure of this oil was supported by ^{1}HNMR.

EXAMPLE 4

1-Carbethoxy-4-[2-(1-methylethoxy)phenyl]piperidine (XVI)

A crude solution of XV (36 g), 10% palladium on carbon (1.80 g) and 5 mL of concentrated methanolic HCl was shaken on a Parr apparatus under 55.5 psig of hydrogen at 22°C for 3 d. The reaction was filtered over Celite, and concentrated to a residue. This material was partitioned between ether and water. The organic solution was dried ($MgSO_4$), filtered, and concentrated to

yield 29.34 g of XVI as a light yellow oil which was carried forward without further purification. The structure was supported by MS and ^{1}HNMR.

EXAMPLE 5

4-[2-(1-Methylethoxy)phenyl]piperidine hydrochloride (XVII)

A mixture of crude XVI (29.3 g) and sodium hydroxide pellets (6.12 g, 0.106 mol) in DMSO (100 mL) was stirred in a preheated oil bath at 100°C for 4 d. The reaction mixture was then poured into a beaker of water (200 mL) and the crude product was extracted into methylene chloride. The methylene chloride extracts were dried over $MgSO_4$, filtered and concentrated to afford 21.34 g of a crude dark brown oil. This oil was dissolved into 1N aqueous HCl solution and washed with ether. The acidic aqueous solution was basified with 3N NaOH and the product as the free base was extracted into methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$), filtered and concentrated to yield 13.34 g of a semi-solid. This material was dissolved in iPrOH and acidified to a pH of 3 with concentrated HCl. The acidified solution was diluted with ether resulting in precipitation of the monohydrochloride salt which was collected by filtration and dried under vacuum to provide 11.21 g of XVII as a beige powder. The structure was supported by MS.

EXAMPLE 6

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperidinyl]methyl]benzoyl]-piperidine hydrochloride (CP #22)

A suspended mixture of XVII (3.75 g, 0.0146 mol), N-[3-(chloromethyl)benzoyl]piperidine (3.45 g, 0.0145 mol) and triethylamine (4.50 mL, 0.0322 mol) in N-methylpyrrolidinone (15 mL) was stirred in a preheated oil

bath (80°C) for 18 h. The reaction mixture was partitioned between methylene chloride and water. The phases were separated. The organic layer was washed with copious amounts of water, dried ($MgSO_4$), filtered and concentrated to afford 5.90 g of a brown oil. Flash chromatography of this material over silica gel using 4% MeOH in chloroform, and conversion to its corresponding HCl salt provided 2.66 g of CP #22 as off-white needles. The structure was supported by ^{1}HNMR, MS, and IR.

Elemental Analysis. Calculated for $C_{27}H_{36}N_2O_2$·HCl: C, 70.95; H, 8.16; N, 6.13; Cl, 7.76. Found: C, 70.69; H, 7.91; N, 5.71; Cl, 7.70.

EXAMPLE 7

4-Fluoro-2-isopropoxy-1-nitrobenzene (XIX)

A suspended orange mixture of 5-fluoro-2-nitrophenol (XVIII, 10.0 g, 63.6 mmol), potassium carbonate (8.84 g, 64.0 mmol) and 2-bromopropane (6.00 mL, 63.6 mmol) in dimethylformamide (63.0 mL) was stirred at 22°C under Argon atmosphere. After 1 d, an additional 2.0 mL of 2-bromopropane was added and the resultant mixture was heated at 60°C for 1 d. The reaction mixture was then partitioned between methylene chloride and 3N NaOH. The organic layer was separated and the basic aqueous layer was extracted with additional methylene chloride. The combined organic solution was washed with water (5 X 200 mL), dried ($MgSO_4$), filtered and concentrated to provide 12.02 g (95%) of an orange oil, 95% pure by GC, which was carried on without further purification. The structure was supported by MS and 90 MHz ^{1}HNMR.

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EXAMPLE 8

4-Fluoro-2-isopropoxyaniline (XX)

A solution of 95% 4-fluoro-2-isopropoxy-1-nitrobenzene (XVIII, 9.50 g, 45.3 mmol) and 10% palladium on carbon (0.50 g) in absolute ethanol (100 mL) was shaken on a Parr apparatus under 53 psig of hydrogen at 22°C for 2 h. The reaction was filtered over Celite, diluted with chloroform, dried ($MgSO_4$), filtered and concentrated to afford 8.37 g of a purple oil, 97% pure by GC, which was carried on without further purification. The structure was supported by GC/MS and ^{1}HNMR.

EXAMPLE 9

1-(4-Fluoro-2-isopropoxyphenyl)piperazine (XXI)

A crude solution of 97% XX (8.35 g, 47.9 mmol), bis-(2-choroethyl)amine hydrochloride (12.83 g, 71.9 mmol) and triethylamine (10.00 mL, 71.7 mmol) in chlorobenzene (70 mL) was heated at reflux for 25 h. The reaction was monitored by capillary GC. The dark brown reaction mixture was then partitioned between 3N NaOH and methylene chloride. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to yield 15.9 g of a brown oil. This crude free base was dissolved in MeOH, treated with fumaric acid (5.25 g), and diluted with ether. The monofumarate salt precipitated out of the mixture and was collected by filtration and dried in a vacuum oven at 60°C to furnish 11.38 g of a brown solid, which was carried on without further purification. The structure was supported by MS and 90 MHz ^{1}HNMR.

EXAMPLE 10

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]-2-piperidone Fumarate (CP #50)

A solution of 2-piperidinone (10.0 g, 0.101 mol), pyridine (16.35 g, 0.207 mol), and benzene (300 mL) was cooled in an ice bath and treated dropwise over 5 min with a solution of 3-(chloromethyl)benzoyl chloride (19.2 g, 0.102 mol). The resulting solution was stirred overnight at ambient temperature. Water (300 mL) was then added. The organic layer was separated, washed with 1N HCl (200 mL) and three 200 mL portions of water, dried ($NaSO_4$), filtered, and concentrated to give 16.5 g of a yellow oil. Addition of ether with cooling afforded 7.25 g of a cream-colored crystalline solid. The H-1 NMR was consistent with the desired structure.

A mixture of the intermediate prepared above (6.25 g, 0.025 mol), N-(2-isopropoxyphenyl)piperazine fumarate (8.40 g, 0.025 mol), potassium iodide (4.50 g, 0.027 mol), triethyl amine (9.57 g, 0.095 mol) and N-methyl-2-pyrrolidinone (50 mL) was stirred for 5.5 h at ambient temperature, treated with water (250 mL), and extracted into ethyl ether (100 mL). The organic layer was separated, dried ($NaSO_4$), filtered, and concentrated to give 6.3 g of an orange oil. This material was purified on 200 g of flash silica gel (EtOAc/methylene chloride, 1:1) to give 3.40 g of CP #50 as a clear oil. Treatment of the oil with fumaric acid (0.90 g) in iPrOH (20 mL) gave a white solid which was recrystallized from iPrOH to give 1.80 g (13%) of CP #50 as a white powder, mp 131.5-133°C. The H-1 NMR in DMSO-d_6 was consistent with the assigned structure assigned structure.

Elemental Analysis. Calculated for $C_{26}H_{33}N_3O_3 \cdot C_4H_4O_4$: C, 65.32; H, 5.76; N, 7.62. Found: C, 65.28; H, 6.87; N, 7.41

In a similar manner, compounds #51, 57, and 70 were prepared by variation of the amide starting material or the aryl piperazine component of the reaction. Specifically, the preparation of compound #51 required the use of 2-azacyclooctanone instead of piperidinone. Compound #57 required the use of N-(methyl)acetamide instead of piperidinone. Compound #70 required the use of N-(2-methoxyphenyl)piperazine instead of IPP and 2-azacyclooctanone instead of piperidinone.

EXAMPLE 11

1-[4-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine Dihydrochloride (CP #11)

A solution of 20 g of N-(2-isopropoxyphenyl)piperazine fumarate was partitioned between aqueous NaOH and methylene chloride. The organic layer was withdrawn and the aqueous layer was washed thrice more with methylene chloride. The organic layers were dried ($MgSO_4$), filtered and concentrated to give 12.5 g of the free base of the piperazine, pure by TLC. This oil was treated with 100 mL of THF, 4-bromobenzyl bromide (16.3 g, 65.3 mmol) and triethylamine (9.1 mL, 65.3 mmol). The solution was stirred at ambient temperature overnight, treated with EtOAc, washed with water, then the product was extracted into 1N HCl (3 times), hexane being added to the organic layer to facilitate the extraction. The combined aqueous extracts were made basic (ca. pH 10, NaOH), and then the product was extracted into methylene chloride (twice), dried ($MgSO_4$), filtered and concentrated to give 20.5 g of a yellow oil (89%). Fast-atom-bombardment MS: m/e 389 (M+1).

A mixture of the oil prepared above (7 g, 18 mmol) and 5.36 mL (54 mmol) of piperidine was treated with $Cl_2Pd(PPh_3)_2$ (0.81 mmol, 4.5 mol %) and heated at 95-105°C under 1 atm. of CO for a period of 8 h. The mixture was

then cooled and treated with water and methylene chloride. The organic layer was withdrawn, dried ($MgSO_4$), filtered and concentrated to give an oil which was purified on two Waters Prep 500 HPLC columns (EtOAc/hexane; 45:55) resulting in 3.35 g yellow oil pure by TLC. This oil was dissolved in iPrOH, filtered through a Millipore filter, treated with concentrated aqueous HCl (1.5 mL), and then triturated with ether. The resulting white solid precipitate was recrystallized from methylene chloride/ether, dried overnight at 70°C under vacuum producing 2.9 g (32%) of CP #11 as a white powder, mp 205-208°C. The ^{1}HNMR in $CDCl_3$ supported the assigned structure.

Elemental Analysis. Calculated for $C_{26}H_{35}N_3O_2 \cdot 2.0HCl \cdot 0.25H_2O$: C, 62.59; H, 7.51; N, 8.42; Cl, 14.21; H_2O, 0.90. Found: C, 62.67; H, 7.83; N, 8.16; Cl, 13.87; H_2O, 2.82.

EXAMPLE 12

1-[2-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine Dihydrochloride (CP #15)

A solution of 2-(bromomethyl)benzoyl bromide (from K and K Laboratories, 12.03 g, 43.28 mmol) in 100 mL of THF was cooled to -78°C under nitrogen gas. The solution was treated with piperidine (4.28 mL, 43.3 mmol) and triethylamine (27.2 mL, 195 mmol). This caused a considerable white precipitate to form. The solution was allowed to slowly warm. When the temperature of the solution was ca. 0°C, N-(2-isopropoxyphenyl)piperazine fumarate (27.2 mL, 195 mmol) was added. The solution was warmed in an oil bath at 70°C for 1 h. The mixture was then treated with water and methylene chloride. The methylene chloride layer was withdrawn, dried ($MgSO_4$), filtered and concentrated to give 24 g of a brown oil. The oil was purified by high-pressure liquid chromatography (hexane/Et_3N, 9:1). This solvent system gave a

fraction which contained 2.5 g of product highly pure by TLC. This was dissolved in iPrOH, filtered through a Millipore filter, and treated with concentrated aqueous HCl (1.13 mL), and the product was triturated with ether. The resultant solid was recrystallized from iPrOH/ether to give 1.7 g of CP #15 as a white powder (8%), mp 192.5-196°C. The ^{1}HNMR in DMSO-d_6 was consistent with the assigned structure.

Elemental Analysis: Calculated for $C_{26}H_{35}N_3O_2 \cdot 2.0HCl$: C, 63.15; H, 7.54; N, 8.50; Cl, 14.34. Found: C, 63.16; H, 7.65; N, 8.63; Cl, 13.92.

In a similar manner, compounds #12-14, 16, and 17 were prepared by variation of the initial amine component in the reaction sequence. Specifically, the preparation of compounds #12, 13, 14, 16 and 17 required the replacement of piperidine with 4-(carbethoxy)piperidine, 3,3-(dimethyl)piperidine, morpholine, N-(methyl)cyclopenylamine, and homopiperidine respectively.

EXAMPLE 13

1-[3-[[4[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]phenylsulfonyl]-4-hydroxypiperidine (CP #21)

N-Bromosuccinimide (6.27 g, 0.035 mole), m-toluenesulfonyl chloride (6.72 g, 0.035 mole), and benzoyl peroxide (0.67 g, 0.0019 mole) were combined in CCl_4 (40 mL) and heated at reflux 2 h. The reaction mixture was filtered and washed with CCl_4. The filtrate was concentrated to give m-bromomethylbenzenesulfonyl chloride, 9.74 g, as a viscous yellow oil.

A mixture of m-bromomethylbenzenesulfonyl chloride (2.50 g, 0.0093 mole), aqueous saturated sodium bicarbonate solution (10 mL), and methylene chloride (20 mL) was cooled to 0-5°C in an ice-water bath and treated with a solution of 4-hydroxypiperidine (0.99 g, 0.0097 mole) and 20 mL of methylene chloride. The resulting mixture was stirred at 0°C for 1 hour, warmed to room

temperature, and stirred overnight. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The organic layers were combined, washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Filtration and evaporation afforded 3.16 g of oil. A solution of this material. N-(2-isopropoxyphenyl)piperazine (2.14 g, 0.0097 mole), N,N-diisopropylethylamine (1.32 g, 1.78 mL, 0.01 mol), and tetrahydrofuran (40 mL) washeated to reflux under argon for 12 h, cooled, and evaporated. The residue was partitioned between methylene chloride and 3N sodium hydroxide solution and the organic layer was separated. Drying over anhydrous magnesium sulfate and evaporation afforded an oil which was purified by chromatography on flash silica, using methanol:ethanol:methylene chloride (1:1:98) as an eluant, to give 1-[3-[[4[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]phenyl sulfonyl]-4-hydroxypiperidine (CP #21). This material was dissolved in diethyl ether and added to a solution of anhydrous hydrochloric acid and diethyl ether. The resulting slurry was filtered, washed with diethyl ether, and stirred in tetrahydrofuran for 1.5 hours. Filtration and drying at 65°C in vacuo afforded 1.90 g (33%) of the hydrochloride salt, m.p. 127-130°C, whose structure was supported by ^{1}HNMR and MS.

Elemental Analysis: Calculated for $C_{25}H_{35}N_3O_4 \cdot 2HCl \cdot H_2O \cdot 0.75$ tetrahydrofuranoate: C, 54.36; H, 7.33; N, 6.79; H_2O, 2.90. Found: C, 54.45; H, 7.53; N, 6.45; H_2O, 2.97.

Using the same synthetic strategy, compounds #18-20 were synthesized by use of the appropriate initial amine component in the reaction sequence. Specifically, the preparation of compounds #18, 19, and 20 required the replacement of 4-hydroxypiperidine with 3,3-(dimethyl)piperidine, piperidine, and pyrrolidine.

EXAMPLE 14

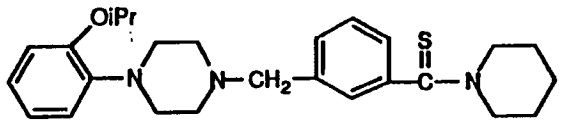
1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]thiobenzoyl]piperidine (CP #1)

A solution of 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]-benzoyl]piperidine (CP #36, 3.86 g, 0.0092 mol) and toluene (50 mL) was treated with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.22 g, 0.0055 mole) and the resulting mixture was heated at 90°C for 1 h. The reaction was cooled followed by the addition of toluene (50 mL), and mixed thoroughly with excess 3N sodium hydroxide solution. The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated to an oily residue. Chromatography of this material on flash silica, using 1.5-2.5% methanol in methylene chloride, afforded CP #1 which was converted to its hydrochloride salt in ethereal hydrochloric acid, 3.61 g (77%), m.p. 221-224°C (dec, uncorrected). The structural assignment was supported by ^{1}HNMR, chemical-ionization MS, and IR data.

Elemental Analysis: Calculated for $C_{26}H_{35}N_3OS \cdot HCl$: C, 61.60; H, 7.30; N, 8.23. Found: C, 61.48; H, 7.47; N, 8.28.

In the Tables and formulas therein OiPr is i-propoxy, Me is methyl, OMe is methoxy, Et is ethyl, Ac is acetyl, Bu is butyl, and Boc is t-butyloxycarbonyl.

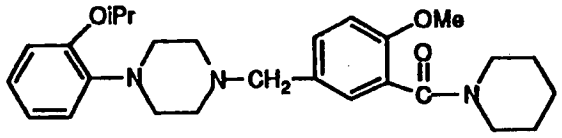
TABLE 1



Comp'd	CAR 5 mg/kg (Escape Loss) IP Administration	Salt Form[1]	M.p. (°C)	Receptor Binding (K_I nM) D2
1	-71% (20%)	2 HCl	221-224	8.0

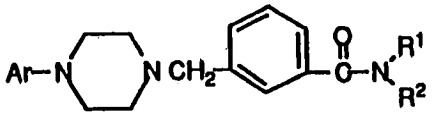
Note: 1. Where solvates were identified by H-1 NMR and elemental analysis in Tables 1-6, they are indicated in parenthesis.

TABLE 2



Comp'd	CAR 5 mg/kg (Escape Loss) IP Administration	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
2	-98% (50%)	2 oxalate (0.75 H_2O)	148-150	32

TABLE 3



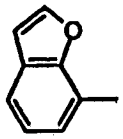
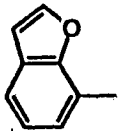
CP	Ar	B1	B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
3			-$(CH_2)_5$-	-82% (19%)	HBr (H_2O)	155-158	15
4			-(CH2)6-	-81% (20%)	HBr (0.5 H_2O)	139-143	14
5			-$(CH_2)_5$-	-90% (8%)	1.1 HCl	243.5-244	41

TABLE 3 (cont'd.)

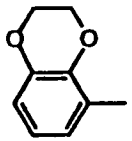
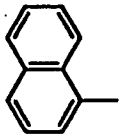
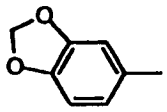
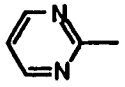
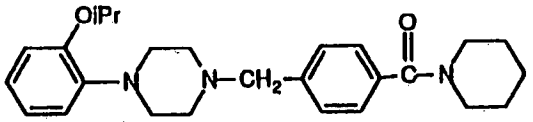
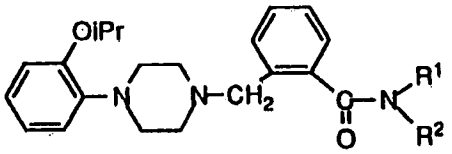
CP	Ar	B1	B2	CAR 5 mg/kg Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
6			-$(CH_2)_5$-	-94% (8%)	1.4 $HClO_4$	150-156	>1000
7	"		-(CH2)6-	-98% (11%) (0.25 H_2O·iPrOH)	1.2 $HClO_4$	134-136	127
8			-$(CH_2)_5$-	-19% (0%) at 15 mg/kg	0.8 maleate	137-140	124
9			-$(CH_2)_5$-	-10% (0%)	oxalate	212-216	>1000
10			-$(CH_2)_5$-	-18% (1%)		107-108	>1000

TABLE 4



Comp'd	CAR 5 mg/kg (Escape Loss) IP Administration	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
11	-35% (6%)	2.0 HCl (0.25 H_2O)	205-208	ca. 100

TABLE 5



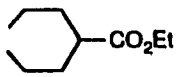
CP #	R_1	R_2	CAR 5 mg/kg Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
12			-0% (0%)	1.8 HCl (0.7 H_2O)	178-182	10.4
			-69% at 15 mg/kg			

Table 5 (cont'd)

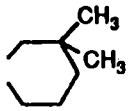
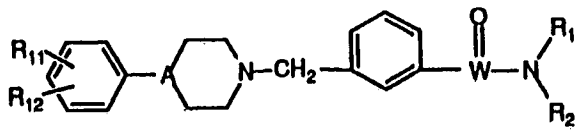
CP #	B1	B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
13			-67% (17%)	2 HCl (H_2O)	214-227	7.0
14			-31% (0%)	2 HCl (0.3 H_2O)	218-220	32
15	-$(CH_2)_5$-		-95% (0%)	2.0 HCl	192.5-196	37
16	CH_3 cC_5H_9		-98% (33%)	2.0 HCl	196-199	16
17	-$(CH_2)_6$-		-72% (12%)	2.0 HCl (0.35 H_2O)	208.5-210.5	11

TABLE 6



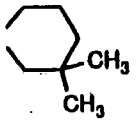
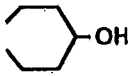
CP #	R11	R12	A	W	R1	R2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
18	2-OiPr	H	N	(S=O)			-4% (2%)	2 HCl	197-202	45
19	"	"	"	"	-$(CH_2)_5$-		-7% (0%)	2 HCl (H_2O)	189-191	18
20	"	"	"	"	-$(CH_2)_4$-		-27% (0%)	-	113-115	196
21	"	"	"	"			-95% (22%)	2 HCl (H_2O)	127-130	69
22	"	"	CH	C	-$(CH_2)_5$-		-92% (5%)	HCl	190-193	2.8
23	"	"	"	"	-$(CH_2)_6$-		-86% (2%)	HCl (0.75 H_2O)	170-172	1.2

Table 6 (cont'd)

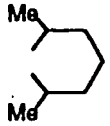
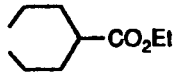
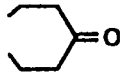
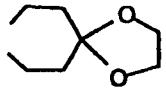
CP #	R11	R12	A	W	R1	R2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
24	2-OiPr	H	CH	C			-98% (37%)	HCl (O.25 H2O)	165-167	NA
25	"	"	"	"	$-(CH_2)_2O(CH_2)_2-$		-96% (70%)	HCl	180-181	9.6
26	"	"	N	C			-18% (0%)	1.35 HCl	210-212	121
27	"	"	"	"	CH_3	$(CH_2)_2Ph$	-6% (0%) -77.0% at 15 mg/kg	oxalate	164-166	19
28	"	"	"	"			-68% (16%)	-	200-202	42
29	"	"	"	"			-95% (20%)	-	102.5-104.3	20
30	2-OMe 5-OMe		"	"	$-(CH_2)_5-$		-66% (48%)	HCl	200-201	592
31	"	"	"	"	$-(CH_2)_4-$		1.5% (0%) (at 15 mg/kg)	HCl	237-238	>1000

Table 6 (cont'd)

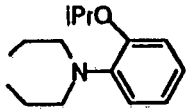
CP #	R11	R12	A	W	R1	R2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (Ki nM) D2
32	2-OMe	6-OMe	N	C		-$(CH_2)_5$-	-1% (1%) (at 15 mg/kg)	1.8 HCl	151-153	>1000
33	3-NO_2	H	"	"		-$(CH_2)_5$-	-1% (1%) -78% at 15 mg/kg	fumarate	194-197	>1000
34	2-OiPr	"	"	"			0% (1%) (0.8 H_2O)	1.3 HCl	197-199	171
35	"	"	"	"		-$(CH_2)_4$-	-98% at 7.5 mg/kg (0%	1.5 HCl	197-199	35
36	"	"	"	"		-$(CH_2)_5$-	-91% at 7.5 mg/kg (8%)	1.5 HCl	222-227	2.2
37	"	"	"	"		-$(CH_2)_6$-	-88% (3%)	HCl	212-214	6.3
38[1]	"	"	"	"		-$(CH_2)_3$-	-88% at 15 mg/kg (0%)	maleate	122-124	NA
39	"	"	"	"		-$(CH_2)_7$-	-93% (27%)	oxalate	172-174	5.3
40	"	"	"	"		-$(CH_2)_2O(CH_2)_2$-	-68% (27%)	1.85 HCl (H_2O)	145-148	95

Table 6 (cont'd)

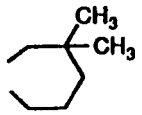
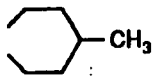
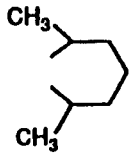
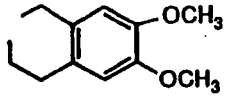
CP #	R11	R12	A	W	R1	R2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (Ki nM) D2
41	2-OiPr	H	N	C			-86% (25%)	oxalate (0.2 H_2O)	156-158	4.8
42	"	"	"	"			-81% (9%)	fumarate	157-158.5	9
43	"	"	"	"		(cis)	-72% (10%)	HCl (0.75 H_2O)	216-218	7.2
44	"	"	"	"			-15% (0%) -93% (7%) at 15 mg/kg	oxalate (0.4 H_2O)	151-154	11

Table 6 - (Cont'd)

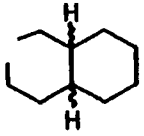
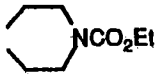
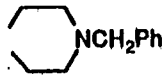
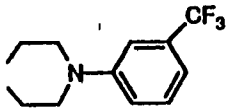
CP #	B11	B12	A	W	B1 B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
45	2-OiPr	H	N	C		-36% (3%)	oxalate	171-173	11.4
46	"	"	"	"		-28% (23%)	3.0 HCl	229-231	10.4
47	"	"	"	"		-20% (1%)	1.1 HCl	205-207	121
48	"	"	"	"		-9% (5.0%) -23% (2%) at 30 mg/kg	2.15 HCl	262-263	40
49	3-CF_3	"	"	"		-3% (0%) -6.6% at 30 mg/kg	2.0 HCl	220-223	ca. 1000
50	2-OiPr	"	"	"	-$C(O)(CH_2)_4$-	-11% (3%) -92% at 15 mg/kg	fumarate	131.5-133	39

Table 6 - (Cont'd)

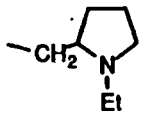
CP #	B11	B12	A	W	B1	B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
51	2-OiPr	H	N	C	-C(O)(CH2)6-		-28% (7%)	fumarate	172-173	10.2
52	"	"	"	"	Et	Et	-96% (14%)	1.5 HCl	175.5-180	14
53	"	"	"	"	nBu	nBu	-5% (0%) -5.6% at 15 mg/kg	1.4 HCl	163-167	16
54	"	"	"	"	nBu	Me	-68% (2%)	1.05 HCl	166-169	15
55	"	"	"	"	cC6H11	H	-18% (0%) -86% at 15 mg/kg	2.0 HCl (H_2O)	170-175	47
56	"	"	"	"	cC6H11	Me	-99% (21%) (iPrOH)	fumarate	170-172.5	5.4
57	"	"	"	"	Ac	Me	-48% (22%)	oxalate	159-161	158
58	"	"	"	"	Me	CH_2Ph	-23% (1%)	oxalate	160-162	13
59	"	"	"	"	4-FPh	H	-0.9% (0%) (at 30 mg/kg)	1.5 HCl	149-151	ca. 30
60	"	"	"	"		H	9% (0%) -75% at 15 mg/kg	2.6 HBr (1.5 H_2O; 0.5 EtOH)	192-195	13.9
61	"	"	"	"	H	H	-89% (27%)	-	172-175	46

Table 6 - (Cont'd)

CP #	R11	R12	A	W	B1	B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
62	2-OiPr	4-F	N	C	$-(CH_2)_5-$		-82% (4%)	1.5 HCl	204-206.5	19
63	"	"	"	"	$-(CH_2)_6-$		-86%(44%) (0.25 H_2O)	HCl	180-184	12
64	"	"	"	"	$-(CH_2)_2O(CH_2)_2-$		-91% (14%)	HCl	206-208	79
65	2-nPr	H	"	"	$-(CH_2)_5-$		1% (0%) 0% (0%) at 15 mg/kg	HCl	190.5-192.5	38
66	2-nPr	"	"	"	$-(CH_2)_6-$		0% (0%) -8% at 15 mg/kg	1.4 $HClO_4$ (0.25H_2O)	157.5-160.5	41
67	2-OEt	"	"	"	$-(CH_2)_6-$		-97% (26%)	HCl	188-190	57
68	2-OMe	"	"	"	$-(CH_2)_5-$		-98% (42%)	2.0 HCl	184-186	29
69	"	"	"	"	$-(CH_2)_6-$		-95% (22%) (1.5 H_2O)	HCl	96-198	201
70	"	"	"	"	$-C(O)(CH_2)_6-$		-1% (0%) -27% (17%) at 15 mg/kg	0.5 fumarate (0.2 H_2O)	112-115.5	121
71	4-Cl	"	"	"	$-(CH_2)_5-$		-1% (0%) -5 %(0%) at 15 mg/kg	2.0 HCl (H_2O)	172-175	>1000
72	2-CF_3	"	"	"	$-(CH_2)_5-$		-5% (0%) -60% (7%) at 15 mg/kg	1.1 HCl	210-211.5	281

Table 6 - (Cont'd)

CP #	B11	B12	A	W	B1	B2	CAR 5 mg/kg (Escape Loss) IP Admin.	Salt Form	M.p. (°C)	Receptor Binding (K_I nM) D2
73	2-Cl	H	N	C		-$(CH_2)_5$-	-13% (0%) -68% at 15 mg/kg	HCl	170-174	77
74	2-CN	"	"	"		-$(CH_2)_5$-	-74% (5%)	0.85 fumarate	182-184	63
75	3-Cl	"	"	"		-$(CH_2)_5$-	-36% (21%)	HCl	183-184	347
76	3-CF_3	"	"	"		-$(CH_2)_5$-	-6% (0%) -72% (3%) at 15 mg/kg	HCl (0.3 H_2O)	207-209	682
77	2-Cl	"	"	"		-$(CH_2)_6$-	-23% (0%)	$HClO_4$	180-183.7	18
78	3-Cl	5-Cl	"	"		-$(CH_2)_5$-	-43% (3%) (0.5H_2O)	HCl	242-248	21
79	H	H	"	"		-$(CH_2)_5$-	-2% (1%) -82% (11%) at 15 mg/kg	HCl	134-136	>1000
80	2-OiPr	"	"	"			-98% (67%) (at 15 mg/kg)	1.1 oxalate (0.1 H_2O)	162-165	NA
81	"	"	"	"	-$(CH_2)_6NH_2$	H	-99% (26%) (at 15 mg/kg)	2 oxalate (0.67 H_2O)	134-136	15
82	"	"	"	"	-$(CH_2)_6$NHBoc	H	-8% (0%) (at 15 mg/kg)	oxalate	131-133	88

1. Three out of four rats found dead 30 min after treatment with CP #38.

TABLE 7

CP	1 h	4 h	IV
#36	0.038 [0.006, 0.056]	0.263 [0.094, 0.439]	0.030 [0.008, 0.045]
#37	0.047 [0.29, 0.86]	0.251 [0.116, 0.801]	0.019[a]
Haloperidol	0.088	0.028[b]	0.023[a]

The ED_{50} (mg/kg) values and 95% confidence limits are shown for oral administration (1 h and 4 h pretreatment) and for intravenous administration. Notes: a. ED_{50} estimated using linear regression, 95% confidence limits not determined. b. ED_{50} computed with PROBIT, 95% confidence limits not determined.

TABLE 8

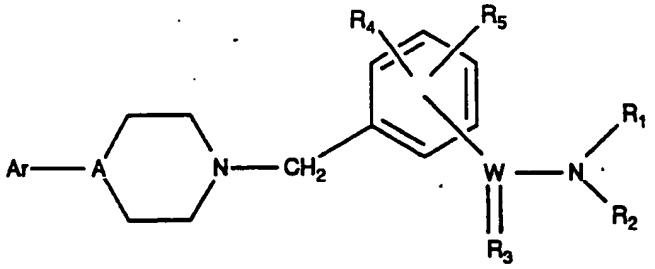
CP #	Dose (mg/kg) (IP Administration)	Pre-Reaction Time (min)	Catalepsy (%)
15	50	60	52
15	50	24	50.7
23	50	60	17.3
36	50	60	32.4
36	50	240	47.9
64	50	60	84.8
64	50	240	62.0
68	50	60	18.8
68	50	240	33.9
77	50	60	20.0
77	50	240	1.9

TABLE 9

CP #	Route of Administration	Dose (mg/kg)	Expiration Time (min)
4	IP	1.0	18
5	IP	1.0	41
6	IP	1.0	10
7	PO	10.0	33
8	PO	10.0	19
9	PO	10.0	7.4
10	PO	10.0	25
11	IP	1.0	43
15	IP	1.0	11
16	IP	1.0	11
17	PO	10.0	15
18	PO	10.0	50
19	PO	10.0	10
34	IP	1.0	14
39	IP	1.0	16
41	IP	1.0	13
42	IP	1.0	15
43	IP	1.0	22
44	IP	1.0	29
45	IP	1.0	43
46	IP	1.0	18
48	IP	1.0	21
49	IP	1.0	41
51	IP	1.0	28
53	IP	1.0	18
56	IP	1.0	14
57	IP	1.0	23
58	IP	1.0	29
59	PO	40.0	25
63	IP	1.0	12
64	IP	1.0	28
65	IP	1.0	17
66	IP	1.0	14
67	IP	1.0	22
68	IP	1.0	16
69	IP	1.0	21
70	IP	1.0	42
72	IP	1.0	22
73	IP	1.0	28
74	IP	1.0	29
75	IP	1.0	16
76	IP	1.0	27
78	IP	1.0	17
79	IP	1.0	25

WE CLAIM:

1. A compound represented by the formula I:



I

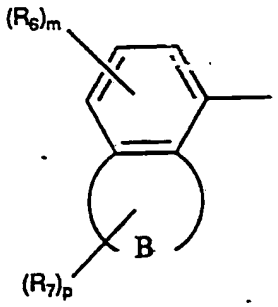
wherein A is N or CH;

wherein W is C or SO;

wherein R_3 is O or S where W is C; R_3 is O where W is SO.

wherein R_1 and R_2 are independently selected from any one of H, C_1-C_8 alkyl, phenyl, substituted phenyl, aralkyl, acyl, C_4-C_{10} cycloalkyl; or $-NR_1R_2$ may be taken together to form a ring, substituted or unsubstituted having 4-10 ring atoms, which ring may be saturated or unsaturated, and may contain one or more hetero atoms selected from S, O or N within the ring; or $-NR_1R_2$ may be taken together to form a spiro ring system, substituted or unsubstituted, which ring system may be saturated or unsaturated; wherein R_4 and R_5 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, NO_2, halogen, haloalkyl, C_1-C_8 alkylthio, amino, or C_1-C_8 mono- or di-alkylamino; wherein Ar is phenyl, heteroaryl, or substituted phenyl or may be a fused ring system which may be substituted or unsubstituted and the acceptable acid addition salts thereof.

2. The compound of claim 1, wherein when Ar is a fused ring system represented by the formula II:



II

wherein B together with the 2 carbon atoms of phenyl group forms an entirely or partly unsaturated cyclic group having 5-7 ring atoms and within the ring 1-3 hetero atoms from any of O, S or N, with the proviso that the sum of the number of O and S atoms is at most 2, and that the N atoms in the ring may be substituted with R_8 selected from any one of H, alkyl, hydroxyalkyl or acyl;

wherein R_6 and R_7 are independently selected from any one of alkyl, C_4-C_{10} cycloalkyl, phenyl, substituted phenyl, heteroaryl, hydroxyalkyl, alkoxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, mono- or diarylamino, hydroxyl, amino, mono- or dialkylamino, carbonyl, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, alkyl-, amino-, or mono-, or dialkylamino-sulphonyl; R_7 may also be oxo or thioxo; m is 0-3 and p is 0-2.

3. The compound of claim 2, wherein B forms together with the two carbon atoms of the phenyl group an entirely or partly unsaturated ring consisting of 5 ring atoms, at least one of which is an oxygen atom;

wherein R_6 and R_7 are independently selected from any one of alkyl, alkoxy, hydroxyl, nitro, cyano, halogen, trifluoromethyl, with the proviso that R_6 is in the meta or ortho position in relation to the piperazine ring; wherein each of m and p has the value of 0-2.

4. The compound of claim 3, wherein m and p each equal 0.

5. The compound of claim 2, wherein when R_6 or R_7 comprise an alkyl group such group contains 1-5 carbon atoms and when R_6 or R_7 comprise a cycloalkyl group the ring system has 3-7 ring atoms and not more than 10 carbon atoms including substituents.

6. The compound of claim 1, wherein Ar is phenyl substituted with an alkoxy group and wherein A is N.

7. The compound of claim 6, wherein the alkoxy group is i-propoxy.

8. The compound of claim 6, wherein W is C, wherein R_3 is O and wherein each of R_4 and R_5 are H.

9. The compound of claim 6, wherein W is O, wherein R_3 is O and wherein each of R_4 and R_5 are H.

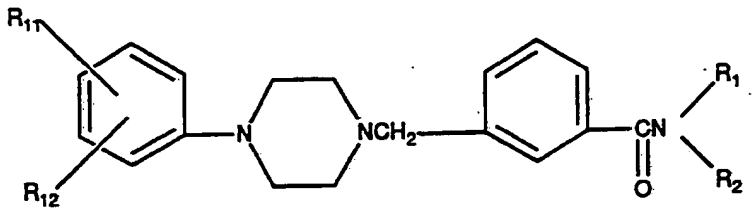
10. The compound of claim 6, wherein W is C, wherein R_3 is S and wherein each of R_4 and R_5, is H.

11. The compound of claim 8, wherein $-NR_1R_2$ are taken together to form a saturated ring having 5-7 carbon ring atoms.

12. The compound of claim 1. wherein Ar is substituted phenyl, and it is substituted with one or more of, C_1-C_8 alkyl, C_1-C_8 alkoxy, cyano, C_1-C_8 alkylthio, halogen, haloalkyl, trifluoromethyl, amino, or mono- or di-alkylamino.

13. The compound of claim 12, wherein Ar is substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, halogen or haloalkyl and wherein $-NR_1R_2$ are taken together to form a saturated ring having 5-7 carbon ring atoms.

14. A compound of the formula I(a):



I a

wherein R_1 and R_2 are independently selected from any one of H, C_1-C_8 alkyl, phenyl, substituted phenyl, C_6-C_{15} aralkyl, C_1-C_8 acyl, C_4-C_{10} cycloalkyl; or $-NR_1R_2$ may be taken together to form a ring, substituted or unsubstituted having 4-10 ring atoms, which ring may be saturated or unsaturated, and may contain one or more hetero atoms selected from S, O, N within the ring; or $-NR_1R_2$ may be taken together to form a spiro ring system, substituted or unsubstituted, which ring system may be saturated or unsaturated;

wherein R_{11} and R_{12} is selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, cyano, C_1-C_8 alkylthio, halogen, haloalkyl, amino, or C_1-C_8 mono- or di-alkyl, and pharmaceutically acceptable acid addition salts thereof.

15. The compound of claim 14 wherein R_{11} is C_1-C_8 alkoxy.

16. The compound of claim 14, wherein NR_1R_2 are taken together to form a ring being containing 5-7 carbon atoms.

17. The compound of claim 14 represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine Hydrochloride (3:2) or any other acid addition salt thereof.

18. The compound of claim 14 represented by the formula hexahydro-1-[[3-[[4-[2-(1-methylethoxy)-phenyl]-1-piperazinyl]-methyl]benzoyl]-1H-azepine Monohydrochloride or any other acid addition salt thereof.

19. The compound of claim 14 represented by the formula 1-[3[[4-(1,4-benzodioxan-5-yl)-1-piperazinyl]-methyl]benzoyl]piperidine Perchlorate (5:7) or any other acid addition salt thereof.

20. The compound of claim 14 represented by the formula 1-[2-[[2-(1-methylethoxy)phenyl-1-piperazinyl]methyl]benzoyl]piperidine Dihydrochloride or any other acid addition salt thereof.

21. The compound of claim 14 represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]-2,6-dimethylpiperidine Hydrochloride or any other acid addition salt thereof.

22. A composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier, said compound being present in a therapeutically effective amount.

23. A method for treating schizophrenia comprising administering to an animal in need of such treatment the compound of claim 1 in an amount sufficient to treat such schizophrenia.

24. A method for treating schizophrenia comprising administering to an animal in need of such treatment the compound of claim 14 in an amount sufficient to treat such schizophrenia.

25. The method of claim 22, wherein R_{11} is C_1-C_8 alkoxy.

26. The method of claim 22, wherein NR_1R_2 are taken together to form a ring being containing 5-7 carbon atoms.

27. The method of claim 22, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]piperidine Hydrochloride (3:2) or any other acid addition salt thereof.

28. The method of claim 22, represented by the formula hexahydro-1-[[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl] methyl]benzoyl]-1H-azepine Monohydrochloride or any other acid addition salt thereof.

29. The method of claim 22, represented by the formula 1-[3[[4-(1,4-benzodioxin-5-yl)-1-piperazinyl]methyl]benzoyl]piperidine Perchlorate (5:7) or any other acid addition salt thereof.

30. The method of claim 22, represented by the formula 1-[2-[[2-(1-methoxyethoxy)phenyl-1-piperazinyl]methyl]benzoyl]piperidine Dihydrochloride or any other acid addition salt thereof.

31. The method of claim 22, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]-2,6-dimethylpiperidine Hydrochloride or any other acid addition salt thereof.

32. The method of claim 22, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperidinyl]methyl]benzoyl]piperidine Monohydrochloride or any other acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09082

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): Please See Attached Sheet.
US CL : Please See Attached Sheet.

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
U.S.	Please See Attached Sheet.

Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched[6]

CAS online

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category*	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
A	US, 4,666,924 (E.I. Du Pont de Nemours & Co.) 19 May 1987. See entire document.	1-32
A	US, 4,772,604 (Duphar International Research B.V.) 20 September 1988, see entire document.	1-32
A	US 4,782,062 (Duphar International Research B.V.) 1 November 1988, see entire document.	1-32
A	US, 4,988,814 (American Home Products Corp.) 29 January 1991, see entire document.	1-32
A	US 4,992,441 (McNeilab, Inc.) 12 February 1991, see entire document.	1-32
A	US, 3,988,371 (Nikdaus R. Hansl) 26 October 1976, see entire document.	1-32
A	US, 4,362,738 (Dr. Karl Thomae (Tmbh) 07 December 1982, see entire document.	1-32
A	US, 4,510,140 (Recordati S.A.) 09 April 1985, see entire document.	1-32
A	US, 4,931,443 (Yoshitomi Pharmaceutical Industries Ltd.) see entire document.	1-32

* Special categories of cited documents:[16]

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
29 MAY 1991	30 JUN 1992
International Searching Authority[1]	**Signature of Authorized Officer**[20]
ISA/US	CECILIA TSANG

Form PCT/ISA/210 (second sheet)(May 1986) ß

FURTHER INFORMATION CONTINUED FROM PREVIOUS SHEETS

I. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

A61K 31/55, 31/535, 31/495, 31/50, 31/47, 31/445, C07D 415/00, 213/62, 401/00, 413/00, 417/00, 419/00, 403/00, 405/00, 409/00, 217/06, 217/12, 411/00, 421/00

I. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/212, 235.5, 235.8, 252, 253; 254, 255, 307, 316, 317, 319, 320, 321, 326, 540/598; 544/120, 295, 357, 360, 361, 368, 370, 372, 376, 377, 393; 546/19, 146, 148, 189, 190, 191, 208.

II. FIELDS SEARCHED
Classification Symbols of Fields Searched:

514/212, 235.5, 235.8, 252, 253, 254, 255, 307, 316, 317, 319, 320, 321, 326;
540/598;
544/120, 295, 357, 360, 361, 368, 370, 372, 376, 377, 393;
546/19, 146, 148. 189, 190, 191, 208.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	JP 62-246,560 (Kanebo KK) 18 April 1986. See formula I.	1-32
Y	US, 4,806,536 (PF1ZER LTD.) 21 February 1989, see example 12(iii).	1,22

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE[1]

1. ☐ Claim numbers _, because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. ☐ Claim numbers _, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. ☐ Claim numbers _, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING[2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.